

CASE REPORT

Open Access



# The drug transporter *ABCB1* c.3435C>T SNP influences artemether–lumefantrine treatment outcome

Kinanga Kiaco<sup>1,3\*</sup>, António Sebastião Rodrigues<sup>4</sup>, Virgílio do Rosário<sup>1</sup>, José Pedro Gil<sup>5</sup> and Dinora Lopes<sup>2,6</sup>

## Abstract

Malaria treatment performance is potentially influenced by pharmacogenetic factors. This study reports an association study between the *ABCB1* c.3435C>T, *CYP3A4*\*1B (g.-392A>G), *CYP3A5*\*3 (g.6986A>G) SNPs and artemether + lumefantrine treatment outcome in 103 uncomplicated malaria patients from Angola. No significant associations with the *CYP3A4*\*1B and *CYP3A5*\*3 were observed, while a significant predominance of the *ABCB1* c.3435CC genotype was found among the recurrent infection-free patients ( $p < 0.01$ ), suggesting a role for this transporter in AL inter-individual performance.

**Keywords:** Human polymorphism, *CYP450*, *MDR1*, Artemether–lumefantrine, Angola

## Background

Artemisinin combination therapy (ACT) has contributed to the remarkable decline by 48% in the malaria mortality rate between 2000 and 2015 [1]. The disease remains a major public health challenge, causing over 400,000 deaths annually, partly due to underperforming treatments. The success of malaria treatment depends on many factors, not least inter-individual pharmacokinetic differences, which are potentially influenced by patient pharmacogenetic background [2].

Artemether–lumefantrine (AL) is the most adopted antimalarial by national malaria control programs worldwide. In Angola, it represents the first-line treatment of choice for uncomplicated malaria.

Upon AL oral administration, artemether shows an elimination half-life of 1–3 h, *CYP3A4* being the main enzyme involved in its conversion towards the (also active) dihydroartemisinin (DHA) metabolite [3]. Both artemether and DHA act rapidly to clear malaria parasites from circulation, reducing asexual parasite mass [4]. The lumefantrine partner has a half-life of 3–6 days and

is responsible for the elimination of parasites remaining from the artemisinin ‘first impact’ action, while preventing recurrent malaria parasitaemia [5]. Only <10% of the absorbed LUM is biotransformed towards the active desbutyl-benflumetol (DBB) metabolite, mainly by *CYP3A* enzymes [6].

Both lumefantrine and DHA are essentially eliminated through the bile. In the apical biliary canalicular membrane of the hepatocyte, the *ABCB1* (*MDR1*/Pgp) ATP-binding cassette (ABC) transporter is a major biliary efflux pump, particularly for lipophilic substrates, as lumefantrine [7, 8]. Significant inter-individual variation in drug exposure is known for both artemisinin and lumefantrine, suggesting the potential importance of *CYP3A4* and *ABCB1* pharmacogenetic characteristics influencing AL performance.

A previous attempt to correlate lumefantrine pharmacokinetic (PK) parameters with *CYP3A4* and *ABCB1* tag SNPs, particularly the promoter located g.-392A>G in the former (*CYP3A4*\*1B) and the synonymous c.3435C>T in the latter, did not yield significant associations [9], having prompted the natural conclusion that such variation had a negligible effect [9]. Possible positive associations were anyway recently suggested for *ABCB1* c.3435C>T with altered LUM exposure among HIV positive subjects under Efavirenz based therapy.

\*Correspondence: kinanga.kiaco@ihmt.unl.pt

<sup>1</sup> Unidade de Parasitologia Médica, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisbon, Portugal  
Full list of author information is available at the end of the article

In the present work, we hypothesized that small pharmacokinetic differences might have observable pharmacodynamic consequences, the parasite reaction being a more sensitive parameter of the individual pharmacogenetic influence. Parasite clearance on day 3 post-treatment, recurrent infection prevalence and the 28-day cure rate endpoint of adequate clinical and parasitologic response (ACPR) were herein used as parameters to assess the effect of the patient pharmacogenetic status on AL in vivo anti-parasite performance. To test this hypothesis, a previously performed AL efficacy trial was analysed.

## Methods

### Patients

One-hundred and three unrelated patients with microscopy confirmed (1000–100,000 asexual parasites/ $\mu$ L) uncomplicated *Plasmodium falciparum* malaria involved in an AL (Coartem<sup>®</sup>, Novartis AG, Basel) efficacy trial in the Luanda region, Angola, conducted during the 2011–2013 period [10]. Briefly, upon informed written consent by the participant or their guardians, patients were treated with weight-adjusted, six-dose AL in 3 days, in accordance with national guidelines [11, 12]. Clinical assessment was performed at D<sub>2</sub>, D<sub>3</sub>, D<sub>7</sub>, D<sub>14</sub>, D<sub>21</sub> and D<sub>28</sub>. At each time-point, thick blood films were examined for the presence of parasites and a capillary blood sample obtained for PCR analysis.

Ethical approval was obtained from the Angolan National Public Health Institute/Ministry of Health Ethics Committee. All procedures followed the latest version of the Declaration of Helsinki.

### Molecular genotyping

Capillary blood sample were collected on filter paper (FTA<sup>®</sup> Classic Card, Whatman). DNA extraction was done by phenol–chloroform methods. The *ABCB1* c.3435C>T, *CYP3A4* g.-392C>G and *CYP3A5* g.6986A>G SNPs were analysed by established PCR–RFLP protocols [13]. Presence of parasitaemia was further tested through the *pfmsp2* PCR amplification of all samples at all time spots [10]. Allele frequencies of the analysed SNPs were compared between groups of patients in accordance with two different treatment outcome phenotypes: (a) *pfmsp2* positive PCR by D<sub>3</sub>, informative concerning the artemisinin partner performance, in accordance with WHO guidelines; and, (b) *pfmsp2* positive PCR during the 28-day follow up (lumefantrine prophylactic effect). The number of clinical failure events (PCR-corrected recrudescence) was too small to warrant their specific analysis. All recrudescences were included in the general recurrence group.

Genotyping data for the parasite *pfmdr1*N86Y SNP, a well-established factor in parasite in vivo response to

AL [14, 15], was available through previously performed PCR–RFLP methods [10].

### Statistical analysis

Data on SNPs were analysed using IBM SPSS version 23. Chi square ( $\chi^2$ ) test and Z statistics were used to determine significant differences between proportions (Graphpad Prism<sup>®</sup> 7, Graphpad Software Inc, La Jolla, CA, USA). Five individual associations were herein tested: recurrence vs *CYP3A4*\*1B allele status, recurrence vs *ABCB1* c.3435C>T SNP status, recurrence vs *CYP3A5*\*3 SNP status, D<sub>3</sub> positivity vs *CYP3A4*\*1B SNP status, and D<sub>3</sub> positivity vs *ABCB1* c.3435C>T SNP status. Accordingly, a Bonferroni-corrected significance threshold at  $p < 0.01$  was considered for these tests. Multivariate Log-linear analysis was performed in order to specifically investigate associations of key three categorical variables: (a) D28 follow-up outcome (recurrence), (b) *ABCB1*/*MDR1* c.3435C>T genotype, and (c) *pfmdr1* N86Y status of the initial infection. The multiple testing was Benjamini–Hochberg corrected, assuming a 10% false discovery rate (q).

### Results

The 28-day PCR-corrected cure rate was 91.3%. On D<sub>3</sub>, 46.6% (n = 48) had positive PCR. During the 28-day follow up, 29/103 patients experienced recurrent parasitaemia, as detected through PCR. Ninety-eight patients were successfully analysed for the *CYP3A4* -392A>G SNP. The genotype frequency in this Angolan population was 0.112 (0.060–0.196, 11/98) for the wild type (g.-392AA), 0.541 (0.438–0.641, 53/98) minor allele homozygous (g.-392GG) and 0.347 (0.438–0.641, 34/98) for the heterozygous (g.-392AG). The population was found in Hardy–Weinberg equilibrium for this locus ( $p > 0.05$ ).

The patient *CYP3A4*\*1B genotype was not found to be significantly associated with either D3 parasite positivity ( $\chi^2 = 5.493$ , df = 1,  $p = 0.019$ ) (Table 1) or treatment outcome upon the 28-day follow up ( $\chi^2 = 2.378$ , df = 1,  $p = 0.123$ ) (Table 2).

Concerning the *ABCB1* c.3435C>T SNP, 101 patients were successfully tested. Genotype frequencies were 0.762 (0.667–0.841, 77/101) for the wild type (c.3435CC), 0.079 (0.035–0.150, 8/101) for the minor allele homozygous (c.3435TT) and 0.158, (0.093–0.244, 16/101) for the heterozygous (c.3435CT). The population was found in Hardy–Weinberg equilibrium for this locus ( $p > 0.05$ ).

The c.3435C>T SNP was also not significantly associated with the D<sub>3</sub> parasite PCR positivity ( $\chi^2 = 0.883$ , df = 1,  $p = 0.347$ ) (Table 1). On the other hand, c.3435TT genotypes were found to be significantly more frequent among patients experiencing recurrent events during follow-up ( $\chi^2 = 6.9693$ , df = 1,  $p = 0.008$ ) (Table 3, Fig. 1).

**Table 1** *CYP3A4-392A>G* and *ABCB1 3435C>T* genotype frequencies and *D*<sub>3</sub> PCR positivity (IC95%)

Gene/SNP	Genotype frequencies (IC 95%)					
	D3 positive			D3 negative		
<i>CYP3A4*1B</i>	AA 3/48 (0.062; 0.016–0.182)	AG 14/48 (0.292; 0.174–0.443)	GG 31/48 (0.646; 0.440–0.775)	AA 8/49 (0.163; 0.078–0.302)	AG 21/49 (0.429; 0.291–0.577)	GG 20/49 (0.408; 0.270–0.558)
<i>MDR1, c3435C&gt;T</i>	CC 34/47 (0.723; 0.571–0.839)	CT 9/47 (0.192; 0.097–0.337)	TT 4/47 (0.085; 0.028–0.213)	CC 41/51 (0.804; 0.665–0.897)	CT 7/51 (0.137; 0.062–0.269)	TT 3/51 (0.059; 0.015–0.172)

NO significant associations were

*D3 positive* positive PCR by day 3; *D3 negative* negative PCR by day 3**Table 2** *CYP3A4-392A>G* and *ABCB1 3435C>T* genotype frequencies and risk of recurrency during the 28-day follow-up (IC95%)

Gene/SNP	Genotype frequencies (IC 95%)					
	Recurrence-free group			Recurrence group		
<i>CYP3A4*1B</i>	AA 8/71 (0.113; 0.053–0.215)	AG 37/71 (0.521; 0.400–0.640)	GG 26/71 (0.366; 0.258–0.490)	AA 3/28 (0.107; 0.028–0.294)	AG 10/28 (0.357; 0.193–0.559)	GG 15/28 (0.536; 0.342–0.720)
<i>ABCB1 3435C&gt;T</i>	CC 60/72* (0.833; 0.723–0.907)	CT 10/72* (0.077; 0.072–0.245)	TT 2/72* (0.028; 0.005–0.106)	CC 17/29* (0.586; 0.391–0.760)	CT 6/29* (0.207; 0.087–0.403)	TT 6/29* (0.207; 0.087–0.403)
<i>CYP3A5*3</i>	AA 46/59 (0.780; 0.653–0.877)	AG 11/59 (0.186; 0.097–0.309)	GG 2/59 (0.034; 0.004–0.117)	AA 17/25 (0.680; 0.465–0.851)	AG 6/25 (0.240; 0.094–0.451)	GG 2/25 (0.080; 0.010–0.260)

\* Significant ( $p < 0.01$ )*Recurrence-free group* without positive PCR during the follow-up days*Recurrence group* with positive PCR during the follow-up days

These changes were further reflected on a significant increase in recurrence risk (OR = 10.59, 1.96–57.30, z-score = 2.739,  $p = 0.006$ ) in this subgroup.

During the completion of the present work, a new report has suggested *CYP3A5* as a contributor to lumen-fantrine metabolism [16]. Following this lead, we have successfully analyzed *CYP3A5\*3* (*c.6986A>G*) in 84 samples, as this is the allele is the most investigated as having a robust deleterious effect in the expression of the gene [17]. Genotype frequencies were 0.750 (0.644–0.838, 63/84) for the wild type (*c.6986AA*), 0.048, (0.013–0.117, 4/84) for the heterozygous (*c.6986AG*) and 0.202 (0.123–0.304, 17/84) for the minor allele homozygous (*c.6986GG*). The sample population was found in Hardy–Weinberg equilibrium for this locus ( $p > 0.05$ ).

As with *CYP3A4\*1B*, no significant association was observed between the patient status for carrying a *CYP3A5\*3* alleles and the parasitological outcome during the 28 day follow up ( $\chi^2 = 0.932$ ,  $df = 1$ ,  $p = 0.335$ ) (Table 2).

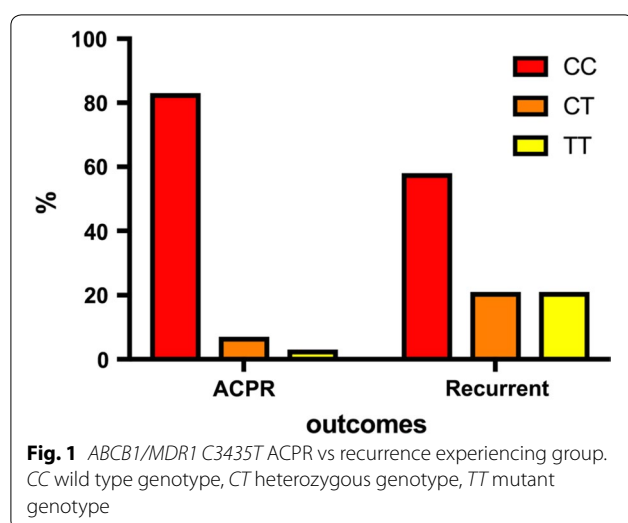
Due to the size limitations of the study, multivariate analysis was limited to variables expected to interact

**Table 3** Analysis of the association between *ABCB1 c.3435C>T* patient status and treatment outcome ( $\chi^2 = 6.9693$ ,  $df = 1$ ,  $p = 0.008$ )

<i>ABCB1 c3435C&gt;T</i>	Recurrence status		Total
	Positive	ACPR	
CC	17	60	77
CT + TT Total	12	12	24
	29	72	101

concerning the clinical outcome under focus (D28 follow up positivity), namely the *ABCB1 c3435C>T* status and the *pfmdr1* N86Y status. A subset of 92 cases was available with complete data for these three variables (Table 4).

Upon the assumption of a false discovery rate of ( $q$ ) of 10% for Benjamini–Hochberg multiple test correction, only two associations stood out as near the threshold of significance: the overall interaction between the three analysed variables ( $G^2 = 10.84$ ,  $df = 4$ ,  $p = 0.0284$  vs  $p$  (corrected) = 0.0286), and the association between recurrence during follow-up and the *ABCB1 c3435C>T* status



**Table 4** Contingency table associated with the Log-linear multivariate analysis

<i>ABCB1</i> <i>c3435C&gt;T</i>	<i>Pfmdr1</i> N86Y	Recurrence status		Total
		Positive (A1)	ACPR (A2)	
CC (B1)	86 N pure (C1)	8	41	49
	86 N/Y + 86Y (C2)	9	11	20
CT + TT (B2)	86 N pure (C1)	9	8	17
	86 N/Y + 86Y (C2)	2	4	6
Total		11	12	92

( $G^2 = 8.36$ ,  $df = 2$ ,  $p = 0.0146$  vs  $p$  (corrected) = 0.0143), after filtering the effect of the presence/absence of the *pfmdr1* N86 allele (Table 4). This analysis further suggests the importance of the *ABCB1 c3435C>T* SNP, albeit the limited number of samples available recommends caution in the interpretation of the results.

## Discussion

The present work focused on finding links between patient *CYP3A* and *ABCB1* pharmacogenetics and AL pharmacodynamics in vivo endpoints.  $D_3$  positivity was not significantly associated with the patient *CYP3A4\*1B* status (Table 1), an observation that can be simply explained by the fact that DHA-the main artemether *CYP3A4* metabolite-is also highly active against *P. falciparum* parasites. Pharmacogenetic driven variable rates of artemether to DHA bioconversion are likely not to be readily visible in terms of the artemisinin effect on the infection. As for the *ABCB1 c3435C>T*, the negative observations possibly result from the specific capacity of this transporter to efflux more lipophilic compounds

then the final phase II glucuronidated DHA extracted from the liver.

The *CYP3A4\*1B* and *CYP3A4\*3* status were not seen to influence the risk of malaria recurrence. The AL post-treatment protective effect is essentially related with the action of lumefantrine, the long half-life partner. In regular conditions, it is expected that the large majority of lumefantrine is eliminated unchanged [18], a result supported by the previously observed modest effect of ketoconazole in interaction studies [6]. This means that any role of *CYP3A4* and/or *CYP3A5* will be limited to variations in this remain biotransformed fraction, which expected small size might have precluded its detection during the present works. One cannot nevertheless rule out the possibility that small changes in the concentrations of the resulting DBB metabolite might influence the treatment, in particular because of its higher anti-parasitic potency, as previously suggested [19]. Also, it is likely that scenarios of long-term *CYP3A* induction might increase the fraction of LUM metabolism-as potentially observed among patients under Efavirenz therapy [20]-and as such the role of this cytochrome P450s on lumefantrine elimination. Nevertheless, inside its size limitations and in this specific population, our study suggests a likely minor contribution of the *CYP3A4\*1B* and *CYP3A5\*3* SNPs in modulating AL post-treatment prophylactic action.

A significant increase in the frequency of the *ABCB1 c.3435TT* genotype was found among patients suffering recurrent infections during the 28-day follow up, suggesting a role of the encoded P-glycoprotein. The synonymous *c.3435C>T* polymorphism has been proposed to be linked with altered rates of protein synthesis, leading to proteins that albeit having the same primary sequence, emerge from the process of translation with different tertiary conformations [21]. The functional effect of such changes in the P-glycoprotein seems to depend on the drug under consideration. In the present studies, a substantial predominance was found of the *ABCB1 c.3435CC* genotype among the recurrence-free patients, signalling an increased lumefantrine exposure associated with this genotype, which better shielded the recovering patients from new infections.

A shortcoming of the present study is the unavailability of pharmacokinetic data, namely  $D_7$  LUM levels, in order to have a complete pharmacokinetic/pharmacogenetic picture. Nevertheless, it is interesting to note that the present results are in agreement with recent data from Maganda et al. [20], where the *ABCB1 c.3435TT* genotype, was suggested to be associated with a significantly decreased  $D_7$  lumefantrine levels among patients undergoing malaria treatment with AL. Such an effect in drug exposure can explain the increase risk of these patients towards recurrent infection.



These data suggest lumefantrine as part of the group of ABCB1 substrates where this genotype is associated with increased drug exposure, probably due to a less efficient efflux. Other examples include tacrolimus [22, 23], silibinin [24], amlodipine [25], or in some studies, digoxine [26].

## Conclusion

By exploring potential pharmacodynamics/pharmacogenetic associations in anti-malarial therapy, this report shows a non-negligible influence of the host *ABCB1* c.3435C>T SNP in the performance of artemether–lumefantrine. The present observations join other recent reports pointing for the importance drug transporter pharmacogenetics in ACT pharmacokinetics and pharmacodynamics [20, 27].

## Authors' contributions

KK participated in the design and implementation of the study in Angola, molecular laboratory work and analysis, data analysis and drafting the manuscript; JPG participated in the analysis of the data, manuscript writing and review; VR and AR reviewed the manuscript, and DL conceived, coordinated and supervised the study. All authors read and approved the final manuscript.

## Author details

<sup>1</sup> Unidade de Parasitologia Médica, Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisbon, Portugal. <sup>2</sup> Global Health and Tropical Medicine (GHTM), Instituto de Higiene e Medicina Tropical, Universidade Nova de Lisboa, Lisbon, Portugal. <sup>3</sup> Serviços de Saúde das Forças Armadas Angolanas, Estado Maior General das Forças Armadas, Luanda, Angola. <sup>4</sup> Centre for Toxicogenomics and Human Health, Genetics, Oncology and Human Toxicology, Universidade Nova de Lisboa, Lisbon, Portugal. <sup>5</sup> Drug Resistance Unit, Division of Pharmacogenetics, Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden. <sup>6</sup> Center for Biodiversity, Functional and Integrative Genomics, Faculdade de Ciências, Universidade de Lisboa, Lisbon, Portugal.

## Acknowledgements

We are sincerely grateful to the patients and parents or guardians of the children involved in the study, as well as the staff of hospitals who participated in sample collection, in particular Mrs Pedro Mbanzulu and Manuel Teca; we thank Lieutenant-General Aires Africano and Lieutenant-General Alcibiades Chindombe of the Angolan Armed Forces for the funding support, as well as Dr. Filomeno Fortes, Dr. Vanda Loa and the Catholic priest Fernando Tchilunda for the useful support provided at the field level. This study received funding from the Angolan Armed Forces. This work was in part funded by the Swedish Research Council Grant Ref. VR-2014-3134.

## Competing interests

The authors declare that they have no competing interests.

## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Consent for publication

Not applicable.

## Ethics approval and consent to participate

Ethical approval was obtained from the Angolan National Public Health Institute/Ministry of Health Ethics Committee. All procedures followed the latest version of the Declaration of Helsinki.

## Funding

This study had a financial support from the Angolan Armed Forces in form of tuition fee allocated to KK. This work was in partly funded by the Swedish Research Council Grant Ref. VR-2014-3134.

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 19 June 2017 Accepted: 30 August 2017

Published online: 21 September 2017

## References

- World Health Organization. World malaria report 2015. Geneva: World Health Organization; 2015.
- Dandara C, Swart M, Mpeta B, Wonkam A, Masimirembwa C. Cytochrome P450 pharmacogenetics in African populations: implications for public health. *Expert Opin Drug Metab Toxicol*. 2014;10:769–85.
- Piedade R, Gil JP. The pharmacogenetics of antimalaria artemisinin combination therapy. *Expert Opin Drug Metab Toxicol*. 2011;7:1185–200.
- World Health Organization. Guidelines for the treatment of malaria. 3rd ed. Geneva: World Health Organization; 2005.
- Djimidé A, Lefèvre G. Understanding the pharmacokinetics of Coartem. *Malar J*. 2009;8(Suppl 1):S4.
- Lefèvre G, Carpenter P, Souppart C, Schmidli H, McClean M, Stypinski D. Pharmacokinetics and electrocardiographic pharmacodynamics of artemether-lumefantrine (Riamet) with concomitant administration of ketoconazole in healthy subjects. *Br J Clin Pharmacol*. 2002;54:485–92.
- Raju KS, Singh SP, Taneja I. Investigation of the functional role of P-glycoprotein in limiting the oral bioavailability of lumefantrine. *Antimicrob Agents Chemother*. 2014;58:489–94.
- Oga EF, Sekine S, Shitara Y, Horie T. Potential P-glycoprotein-mediated drug-drug interactions of antimalarial agents in Caco-2 cells. *Am J Trop Med Hyg*. 2012;87:64–9.
- Staepli-Hodel EM, Csajka C, Ariei F, Guidi M, Kabanyanyi AM, Duong S, et al. Effect of single nucleotide polymorphisms in cytochrome P450 isoenzyme and N-acetyltransferase 2 genes on the metabolism of artemisinin-based combination therapies in malaria patients from Cambodia and Tanzania. *Antimicrob Agents Chemother*. 2013;57:950–8.
- Kiaco K, Teixeira J, Machado M, do Rosário V, Lopes D. Evaluation of artemether-lumefantrine efficacy in the treatment of uncomplicated malaria and its association with pfmdr1, pfatpase6 and K13-propeller polymorphisms in Luanda, Angola. *Malar J*. 2015;14:504.
- WHO. World malaria report 2016. Geneva: World Health Organization; 2016.
- Fançony C, Brito M, Gil JP. *Plasmodium falciparum* drug resistance in Angola. *Malar J*. 2016;15:74.
- Cavaco I, Gil JP, Gil-Berglund E, Ribeiro V. CYP3A4 and MDR1 alleles in a Portuguese population. *Clin Chem Lab Med*. 2003;41:1345–50.
- Malmberg M, Ferreira PE, Tarning J, Ursing J, Ngasala B, Björkman A, et al. *Plasmodium falciparum* drug resistance phenotype as assessed by patient antimalarial drug levels and its association with pfmdr1 polymorphisms. *J Infect Dis*. 2013;207:842–7.
- Venkatesan M, Gadalla NB, Stepniewska K, Dahal P, Nsanabana C, Moriera C, et al. Polymorphisms in *Plasmodium falciparum* chloroquine resistance transporter and multidrug resistance 1 genes: parasite risk factors that affect treatment outcomes for *P. falciparum* malaria after artemether-lumefantrine and artesunate-amodiaquine. *Am J Trop Med Hyg*. 2014;91:833–43.
- Mutagonda RF, Kamuhabwa AAR, Minzi OMS, Massawe SN, Asghar M, Homann MV, et al. Effect of pharmacogenetics on plasma lumefantrine pharmacokinetics and malaria treatment outcome in pregnant women. *Malar J*. 2017;16:267.
- Kuehl P, Zhang J, Lin Y, Lamba J, Assem M, Schuetz J, et al. Sequence diversity in CYP3A promoters and characterization of the genetic basis of polymorphic CYP3A5 expression. *Nat Genet*. 2001;27:383–91.
- Cousin M, Kummerer S, Leefvre G, Marrast AC, Stein D, Weaver M. Coartem (artemether-lumefantrine) tablets for the treatment of malaria in patients with acute, uncomplicated infections due to *Plasmodium falciparum* or mixed infections including *P. falciparum*. Advisory Committee Briefing Book, Novartis, October 2008.
- Wong RP, Salman S, Ilett KF, Siba PM, Mueller I, Davis TM. Desbutyl-lumefantrine is a metabolite of lumefantrine with potent in vitro antimalarial

- activity that may influence artemether-lumefantrine treatment outcome. *Antimicrob Agents Chemother*. 2011;55:1194–8.
20. Maganda BA, Minzi OM, Ngaimisi E, Kamuhabwa AA, Aklillu E. CYP2B6\*6 genotype and high efavirenz plasma concentration but not nevirapine are associated with low lumefantrine plasma exposure and poor treatment response in HIV-malaria-coinfected patients. *Pharmacogenom J*. 2016;16:88–95.
  21. Kimchi-Sarfaty C, Oh JM, Kim IW, Sauna ZE, Calcagno AM, Ambudkar SV, et al. A “silent” polymorphism in the MDR1 gene changes substrate specificity. *Science*. 2007;315:525–8.
  22. Cheung CY, Op den Buijsch RA, Wong KM, Chan HW, Chau KF, Li CS, et al. Influence of different allelic variants of the CYP3A and ABCB1 genes on the tacrolimus pharmacokinetic profile of Chinese renal transplant recipients. *Pharmacogenomics*. 2006;7:563–74.
  23. Kravljaca M, Perovic V, Pravica V, Brkovic V, Milinkovic M, Lausevic M, et al. The importance of MDR1 gene polymorphisms for tacrolimus dosage. *Eur J Pharm Sci*. 2016;83:109–13.
  24. Tan ZR, Zhou YX, Liu J, Huang WH, Chen Y, Wang YC, et al. The influence of ABCB1 polymorphism C3435T on the pharmacokinetics of silibinin. *J Clin Pharm Ther*. 2015;40:685–8.
  25. Kim KA, Park PW, Park JY. Effect of ABCB1 (MDR1) haplotypes derived from G2677T/C3435T on the pharmacokinetics of amlodipine in healthy subjects. *Br J Clin Pharmacol*. 2007;63:53–8.
  26. Sakaeda T, Nakamura T, Horinouchi M, Kakumoto M, Ohmoto N, Sakai T, et al. MDR1 genotype-related pharmacokinetics of digoxin after single oral administration in healthy Japanese subjects. *Pharm Res*. 2001;18:1400–4.
  27. Vos K, Sciuto CL, Piedade R, Ashton M, Björkman A, Ngasala B, Mårtensson A, Gil JP. MRP2/ABCC2 C1515Y polymorphism modulates exposure to lumefantrine during artemether-lumefantrine antimalarial therapy. *Pharmacogenomics*. 2017;18:981–5.

Submit your next manuscript to BioMed Central and we will help you at every step:

- We accept pre-submission inquiries
- Our selector tool helps you to find the most relevant journal
- We provide round the clock customer support
- Convenient online submission
- Thorough peer review
- Inclusion in PubMed and all major indexing services
- Maximum visibility for your research

Submit your manuscript at  
[www.biomedcentral.com/submit](http://www.biomedcentral.com/submit)

